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Thioether-phosphite: new ligands for the highly enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins†

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We have described the first successful application of non-N-donor heterodonor ligands—thioether-phosphite ligands—in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Excellent enantioselectivities (ee's up to 99%) have been obtained for a range of substrates, including challenging terminal disubstituted substrates, under standard conditions.

Pharmaceuticals, agrochemicals, fragrances, fine chemicals, and natural product chemistry all rely on enantiomerically enriched compounds. Because of their high efficiency, atom economy and operational simplicity, the asymmetric hydrogenation of properly selected prochiral starting materials could be a sustainable and direct synthetic tool for preparing these compounds.[1] For many years now olefins containing an adjacent polar group (*i.e.* dehydroamino acids) have been successfully reduced by Rh- and Ru-catalyst precursors modified with phosphorus ligands, but the asymmetric hydrogenation of minimally functionalized olefins is less developed because these substrates have no adjacent polar group to direct the reaction.[1]

In the last decade, Ir complexes containing chiral P,N-ligands emerged as powerful tools in the asymmetric hydrogenation of minimally functionalized olefins.[2] They were essentially complementary to Rh– and Ru–diphosphine catalysts. Due to the early success of Pfaltz *et al.*[3a] and others[3b–e] in developing chiral heterodonor phosphine–oxazoline ligands as chiral mimics of Crabtree's catalyst $[Ir(cod)(py)(PCy_3)]PF_6$,[4] research in this field has focused on maximizing the efficiency of these ligands by: (i) modifying the structure of the chiral ligand's backbone, (ii) replacing the phosphine moiety with a phosphinite, phosphite or carbene group and (iii) changing the oxazoline moiety for other N-donor groups (such as oxazole, pyridine or thiazole).[5] However, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has never been contemplated.

In this communication, we report a new class of non-N-donor heterodonor ligands—thioether-phosphite(Fig. 1)—for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.[6,7] These ligands are derived from natural D-xylose and they combine the advantages of phosphite and sugar cores: that is to say, they are readily available from cheap feedstocks, are highly resistant to oxidation, and have a straightforward modular construction.[8] Moreover, the introduction of a thioether moiety in the ligand design may be beneficial because: (i) the S atoms become a stereogenic center when coordinated to the metal, which moves the chirality closer to the metal, and (ii) the thioether group is more stable than the oxazoline moiety.[9] The highly modular construction of these ligands makes it easy for us to study four main effects on catalytic activity and selectivity: (a) the effect of systematically varying the position of the thioether group at either C-5 (ligands **L1–L6**) or C-3 (ligands **L7–L8**) of the furanoside backbone, (b) the effect of the configuration at C-3 of the furanoside backbone, (c) the effect of the substituents in the thioether group (**L1–L4**) and (d) the effect of the substituents and configurations in the biaryl phosphite moiety (**a–d**). By carefully selecting these ligand parameters, we achieved high enantioselectivities for a range of substrates, including challenging terminal disubstituted substrates.

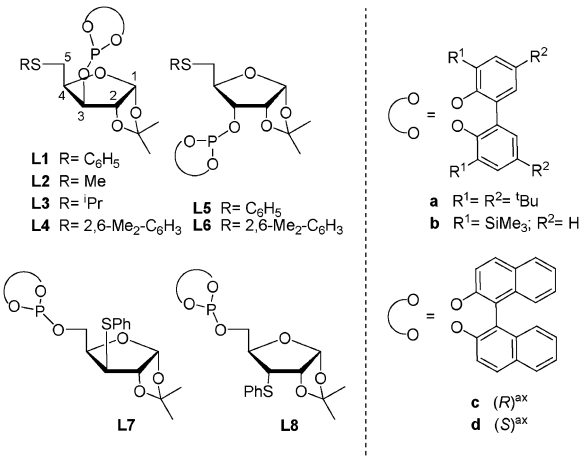

Fig. 1 Thioether-phosphite ligands **L1–L8a–d**.

The synthesis of the phosphite-thioether ligands **L1–L8a–d** is straightforward (Scheme 1).[10] They were efficiently synthesized by reacting the corresponding sugar hydroxyl-thioether (**5–10**, **12** and **14**) with 1 equiv. of the corresponding biaryl

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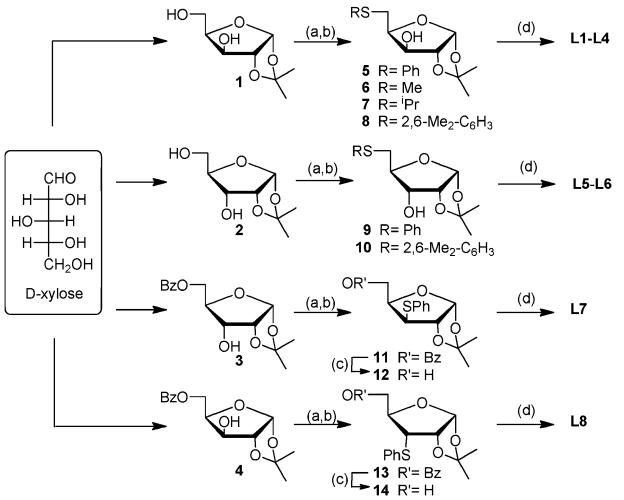
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of new ligands and $[Ir(cod)(\mathbf{L})]BAr_F$ (**L** = **L1–L8a–d**) complexes. See DOI: 10.1039/c1cc13300d



Scheme 1 Synthesis of thioether-phosphite ligands **L1–L8a–d**. (a) Tf_2O, Py, CH_2Cl_2, −15 °C; (b) NaSR, THF, rt; (c) NH_4OH/MeOH; (d) $ClP(OR)_2$, Py, toluene, 80 °C.

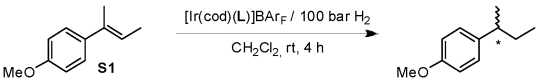
phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a–d**) in the presence of pyridine (Scheme 1, step (d)). Compounds **5–10**, **12** and **14** were synthesized very efficiently from the corresponding easily accessible sugar-derived alcohols **1–4**. These latter compounds are easily prepared on a large scale from inexpensive D-xylose.[11] Compounds **1–4** were treated with one equiv. of triflic anhydride to produce the desired monotriflates. Subsequent reaction with the corresponding NaSR provided direct access to the corresponding hydroxyl-thioether **5–10** and benzoyl-thioether intermediates **11** and **13** (Scheme 1, step (a, b)). The benzoyl protecting group of compounds **11** and **13** was removed under basic standard conditions to obtain hydroxyl-thioethers **12** and **14** (Scheme 1, step (c)). All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in good yields as white solids.

The Ir-catalyst precursors [Ir(cod)(**L**)]BAr_F (L = **L1–L8a–d**) were made by refluxing a dichloromethane solution of the appropriate ligand in the presence of 0.5 equiv. of $[Ir(\mu\text{-}Cl)(cod)]_2$ for 1 h followed by counterion exchange with sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (1 equiv.) in the presence of water (eqn (1)).

$$[Ir(\mu\text{-}Cl)(cod)]_2 \xrightarrow[2)NaBAr_F/H_2O]{1)\mathbf{L}/CH_2Cl_2} 2[Ir(cod)(\mathbf{L})]BAr_F + 2cod \quad (1)$$

All complexes were isolated as air-stable red-orange solids and were used without further purification. VT-NMR (+40 °C to −70 °C) experiments indicate the presence of a single isomer in all cases except for [Ir(cod)(**L1–L4a–d**)]BAr_F in which two isomers are present. These isomers may be attributed to the two possible diastereoisomers formed when the thioether coordinates to the metal atom (note that the coordinated S atom is a stereogenic center), to the different tropoisomers of the biphenyl moieties, or to both. However, comparing compound Ir/**L1a** with related compounds Ir/**L1c** and Ir/**L1d**, which contain enantiomerically pure binaphthyl moieties, the presence of two isomers in them all suggests that these isomers are due to the different configurations of the sulfur stereocentre.

Table 1 Selected results for the Ir-catalyzed asymmetric hydrogenation of **S1** using ligands **L1–L8a–d**[a]



Entry	L	mol% Ir	% Conv.[b]	% ee[b]
1	**L1a**	2	100	13 (*R*)
2	**L2a**	2	100	15 (*R*)
3	**L3a**	2	100	23 (*R*)
4	**L4a**	2	100	30 (*R*)
5	**L5a**	2	100	87 (*R*)
6	**L5b**	2	100	87 (*R*)
7	**L5c**	2	100	26 (*R*)
8	**L5d**	2	100	24 (*R*)
9	**L6a**	2	100	99 (*R*)
10	**L7a**	2	100	68 (*R*)
11	**L8a**	2	100	68 (*S*)
12	**L6a**	0.5	82	99 (*R*)

[a] Reactions carried out using 1 mmol of **S1**. [b] Conversion and enantiomeric excesses determined by chiral GC.

From this we can also conclude that ligand backbones **L5–L8** effectively control the thioether coordination to iridium leading to the formation of a single diastereoisomer.

In the first set of experiments, we used the Ir-catalyzed hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene **S1** to scope the potential of ligands **L1–L8a–d**. The results are summarized in Table 1 and indicate that enantioselectivity is highly affected by the position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituent and the substituents in the biaryl phosphite moiety (**a–d**). We therefore found a cooperative effect between the position of the thioether group and the configuration of carbon atom C-3 of the furanoside backbone (Table 1, entries 1, 5, 10 and 11). The results indicate that the matched combination is achieved with ligands **L5–L6**, which have the thioether moiety attached to C-5 and an *R* configuration of carbon atom C-3 (entries 5 and 9). We also found that bulky substituents need to be present in both the biaryl phosphite (entries 5, 6 *vs.* 7, 8) and the thioether (entries 5 *vs.* 9) moieties if enantioselectivities are to be high. It should be noted that the configuration of the biaryl phosphite group has little effect on the enantioselectivity (entries 7 and 8). Excellent enantioselectivity (99% ee, entry 9) was therefore obtained using the Ir–**L6a** catalytic system, which contains the optimal combination of ligand parameters.

We also performed the reaction at low catalyst loading (0.5 mol%) using ligand **L6a** (entry 12). The excellent enantioselectivity (99% (*R*) ee) was maintained.

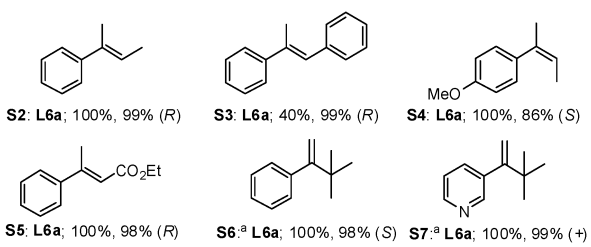


Fig. 2 Selected hydrogenation results. Reaction conditions: 2 mol% catalyst, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. [a]1 bar H_2.

To study the potential of these readily available ligands in greater depth, we also tested them in the asymmetric hydrogenation of several other minimally functionalized olefins (Fig. 2). The enantioselectivities are among the best observed for these substrates.[2] As expected Ir–**L6a** also provides high levels of enantioselectivities (99% ee) in the reduction of other trisubstituted *E*-olefins (**S2** and **S3**). Notably, high enantioselectivities can also be obtained for the more demanding *Z* isomer **S4**, which usually reacts with much lower enantioselectivity than that of the corresponding *E*-isomer **S1**. Ir–**L6a** also proved to be an excellent catalyst for the hydrogenation of α,β-unsaturated ester **S5** (98% ee). It should be noted that this novel class of catalyst precursors also proved to be highly effective in one of the most challenging classes of substrates—the 1,1-disubstituted terminal olefins.[12] Thus, excellent enantioselectivities (98–99% ee) were achieved in the reduction of aromatic and heteroaromatic terminal substrates **S6** and **S7** under mild reaction conditions (1 bar of H_2).

In summary, we have described the first successful application of non-N-donor heterodonor ligands—thioether-phosphite ligands—in the Ir-catalyzed asymmetric hydrogenation of several minimally functionalized olefins. These ligands combine the advantages of phosphite, thioether and sugar cores: that is to say, they are readily available from cheap feedstocks, are more resistant to oxidation than phosphines and phosphinites, and are more stable than oxazolines. In addition, they can be easily tuned in the sugar core, the thioether and biaryl phosphite moieties so that their effect on catalytic performance can be explored. By carefully selecting the ligand components, we obtained high enantioselectivities under unoptimized reaction conditions. This is an exceptional ligand family, which is able to reduce in excellent ee's (up to 99%) a range of *E*- and *Z*-trisubstituted and disubstituted substrate types. These results provide a new class of ligands for the highly enantioselective Ir-catalyzed hydrogenation of a wide range of substrates and open up the enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins to a type of ligand other than N-donor heterodonor ligands. Mechanistic studies are currently under way and further applications are being looked into.

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